Determination of radionuclidic impurities in 99mTceluate from 99Mo/99mTc generator for quality control

Hou, Xiaolin

Published in:
Journal of Radioanalytical and Nuclear Chemistry

Link to article, DOI:
10.1007/s10967-017-5369-9

Publication date:
2017

Document Version
Peer reviewed version

Determination of Radionuclidic Impurities in ^{99m}Tc Eluate from ^{99}Mo-^{99m}Tc Generator for Quality Control

Xiaolin Hou

Center for Nuclear Technologies, Technical University of Denmark, Risø Campus, 4000 Roskilde, Denmark

Abstract

Technetium-99m is the principal radioisotope used in medical diagnostics; radionuclidic impurity is the major concern of its quality. This work presents a analytical method for sequential determination of all radionuclidic impurities listed in pharmacopoeia including gamma emitters, alpha emitters, ^{89}Sr and ^{90}Sr. Radioactive decay for removal of ^{99m}Tc, ion exchange and extraction chromatography for removal of ^{99}Mo and ^{99}Tc are effective for separation of interferences. Gamma spectrometry, LSC with alpha/beta discrimination, and Cherenkov counting using LSC are sensitive methods for measurement of the impurity radionuclides. The detection limits of this method are well meet the requirement of the quality control according to the limitation of the pharmacopoeia.

Keywords

Radionuclidic impurity, ^{99}Mo/^{99m}Tc generator; ion exchange; extraction chromatography; liquid scintillation counting; alpha-beta discrimination; Cherenkov counting

Introduction

Technetium-99m is the principal radioisotope used in medical diagnostics; more than 30 million ^{99m}Tc procedures are used per year all over the world, which accounts for about 80% of all nuclear medical diagnoses. ^{99m}Tc is mainly provided through ^{99}Mo/^{99m}Tc generator [1], although it can be also directly produced through ^{100}Mo(p,2n)^{99m}Tc reaction by proton irradiation of stable ^{100}Mo in a cyclotron [2]. ^{99}Mo used in the generator can be produced by neutron irradiation of stable ^{98}Mo or through neutron-induced fission of ^{235}U using enrich ^{235}U target. Due to the high specific radioactivity of ^{99}Mo produced by fission of ^{235}U (>10^{14} Bq/g Mo), ^{99}Mo in most of generators used for nuclear medical purpose are produced by irradiation of enrich ^{235}U in nuclear reactor. After irradiation of enriched ^{235}U, large number of radionuclides including all fission products and many neutron activation products are produced; ^{99}Mo has to be separated from uranium matrix and all other radionuclides before loading to the alumina column in ^{99}Mo/^{99m}Tc generator. The radionuclidic impurity in ^{99m}Tc eluate (sodium pertechnetate injection) used in the nuclear medicine, especially the long-lived radionuclides, is a major concern in the application of this product, because these impurities might interfere the efficiency of diagnosis and therapy, meanwhile the injection of radionuclidic impurities will also cause an extra radiation to the patients. Among all radionuclides produced in the irradiated ^{235}U, ^{131}I, ^{103}Ru, ^{89}Sr, ^{90}Sr and alpha emitters (uranium, plutonium, neptunium, americium and curium isotopes) are the most important ones because of their high production rates (high fission yield), relative long half-life and high radiation/chemical toxicity (especially alpha emitters). In the ^{99m}Tc eluate from ^{99}Mo/^{99m}Tc generator, ^{99}Mo is the most important radionuclidic impurity, which might breakthrough the column of the generator, and cause extraordinary radiation to the patient due to their relative longer half-life (65.9 h) compared to ^{99m}Tc (6 h). Therefore, it is required by the medical authorities that ^{99m}Tc eluate from the ^{99m}Tc-^{99}Mo generator has to contain limited amount of radionuclides other than ^{99m}Tc. According to Ph.Eu Monograph, the major concerning radionuclides in the sodium pertechnetate injection (^{99m}Tc eluate) from a ^{99m}Tc-^{99}Mo generator using fission ^{99}Mo include ^{99}Mo, ^{131}I, ^{103}Ru, ^{89}Sr, ^{90}Sr, alpha emitting impurities and other gamma (beta) emitting impurities. Table 1 listes the limitation of these impurities in the European and US pharmacopoeias. Except

^{99}Mo, the limitations for other impurities are the same for these two pharmacopoeias [3, 4].

Table 1 Limitation of radionuclidic impurities in ^{99m}Tc eluate by pharmacopoeias

Radionuclide	Half life	γ-rays energy (keV)	βmax Energy (MeV)	Limitation, ratio to ^{99m}Tc by pharmacopoeias	
				EU [3]	US [4]
^{99}Mo	65.9 h	739.5(12.2%)	1.350	1×10^{-3}	1.5×10^{-4}
^{131}I	8.02 d	364.4(81.7%)	0.971	5×10^{-5}	5×10^{-5}
^{103}Ru	39.3 d	497.1(91%)	0.763	5×10^{-5}	5×10^{-5}
^{89}Sr	50.5 d		1.495	6×10^{-7}	6×10^{-7}
^{90}Sr	28.7 y		0.546	6×10^{-8}	6×10^{-8}
α-emitters				1×0^{-9}	1×0^{-9}
All other γ-emitters				1×10^{-4}	
All other γ and β-emitters					1×10^{-4}

In the routine analysis for quality control of ^{99m}Tc eluate, only ^{99}Mo is often measured using lead shield (6 mm) of sample and dose calibrator measurement [1, 5, 6]. This is based on the higher gamma energy of ^{99}Mo (739.5 keV, 777.9 keV) compared to ^{99m}Tc (140.5 keV), most of ^{99m}Tc (>99%) can be shielded, but the counting efficiency of ^{99}Mo is only reduced by 50%. A few methods have also been reported to measure ^{89}Sr and ^{90}Sr in the ^{99m}Tc eluate using complicated ion exchange chromatography, solvent extraction, active charcoal adsorption, oxalate/sulfate precipitation and extraction chromatography for separation and liquid scintillation counting (LSC) or proportional counter for measurement of ^{89}Sr and ^{90}Sr [7-9]. Some methods have also been reported to separate alpha emitters including plutonium, uranium and americium from ^{99m}Tc eluate and to measure them using alpha spectrometry or LSC with alpha/beta discrimination [10-12]. Most of these methods are tedious and complicated. No method for sequentially separation of these radionuclides and measurement of them with sufficient detection limit

has been reported. This work aims to establish an analytical method by sequentially separation of target radionuclides followed by sensitive measurement using LSC for quality control analysis of all radionuclidic impurities listed in Table 1 in ^{99m}Tc eluate from ^{99}Mo/^{99m}Tc generator.

Experimental

Materials, Standards and chemical reagents

Strong basic anion exchange resin AG1×4, Cl^- form, 50-100 mesh was purchased from Bio-Rad Laboratories, Inc. (California, UAS), 2 mL plastic empty column and Sr-resin in 2 ml plastic column (100-150 μm) was purchased from TRISKEM International (Bruz, France), 20 mL glass vials and liquid scintillation cocktail Ultima Gold LLT was purchased from PerkinElmer Inc (Massachusetts, USA). All chemicals used in the experiment were of analytical grade and prepared using deionized water (18.2 MΩ). ^{85}Sr and ^{241}Am solutions were provided by Hevesy laboratory, Technical University of Denmark. Uranium standard solution was purchased from LabKings B.V (Hilversum, the Netherlands). The standard solutions of ^{99}Mo, ^{131}I, ^{103}Ru, ^{89}Sr, ^{90}Y and ^{90}Sr were provided and certified by Eckert & Ziegler Analytics, California, USA), ^{242}Pu standard solution (NIST-4334G) was purchased from National Institute of Standard and Technology (Gaithersburg, MD, USA).

Sequential separation for separation of interfering radionuclides

The radioactivity of impurity radionuclides is normally 3-9 orders of magnitude lower than ^{99m}Tc in the ^{99m}Tc eluate. It is impossible to directly measure these impurity radionuclides using radiometric methods, Removal of most of ^{99m}Tc is needed for measurement of other gamma emitters. Most of radionuclides has to be separated for measurement of alpha emitters, and determination of low level ^{89}Sr and ^{90}Sr requires a completely removal of all other radionuclides except strontium. Fig. 1 presents a schematic diagram of sequential separation/removal procedure for determination of the radionuclidic impurities in ^{99m}Tc eluate. The detailed procedures are presented below.

Removal of ^{99m}Tc for measurement of γ emitters

Based on the relative short half-life of ^{99m}Tc (6.02 h) compared to other impurity radionuclides (>65 h), ^{99m}Tc was removed by more than 7 days decay. The ^{99m}Tc eluate of 5 ml was divided into two aliquots; one 2 ml aliquot was transferred to a 10 ml glass vial, which was stored in a lead pot. After 5-10 days decay, this aliquot was directly measured using γ-spectrometry for all gamma emitters including ^{99}Mo, ^{131}I and ^{103}Ru.

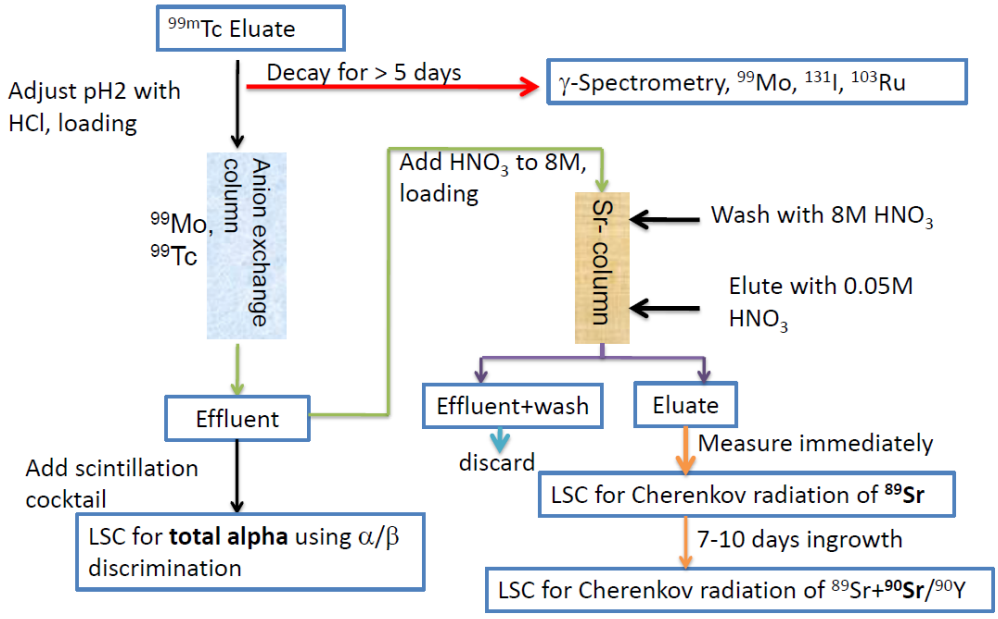


Fig.1 Schematic diagram of the sequential separation procedure for determination impurity radionuclides in ^{99m}Tc eluate

Remove of ^{99m}Tc and ^{99}Mo using anion exchange chromatography and Sr resin.

Alpha emitters including isotopes of uranium, plutonium, neptunium, americium and curium were measured using LSC employing the α/β discrimination function. Some beta particles might be spillover into alpha window in LSC measurement, meanwhile the content of alpha emitters is very low in the ^{99m}Tc eluate. ^{99m}Tc and ^{99}Mo were removed using anion exchange chromatography based on the high adsorption of TcO_4^- and MoO_4^{2-} on the column at neutral and low acidic solution, but no significant adsorption of

actinides on the column in this condition. Because ^{89}Sr and ^{90}Sr are cation in ^{99m}Tc eluate, they were also collected in the effluent. The recovery of actinides and strontium in separation procedure using anion exchange resin was investigated using ^{242}Pu, uranium, ^{85}Sr, ^{90}Sr and ^{90}Y as tracers.

1.9 mL of 0.9% NaCl solution was transferred to a beaker, 0.20 ml of 1.0 mol/l HCl solution and 0.10 ml of individual radionuclides (^{85}Sr, ^{90}Sr-^{90}Y, ^{90}Y, ^{99m}Tc, ^{99}Mo, ^{242}Pu, uranium and ^{241}Am) was spiked to the beaker. The spiked solution was loaded to a 2ml AG1-×4 anion exchange column (50-100 mesh) preconditioned with 5 ml of 0.9% NaCl-0.1 mol/l HCl. The beaker was washed 2 times using 1.0 ml of 0.10 mol/l HCl solution each and the wash solution was loaded to the column. The effluent and washes were collected and combined in a vial. Standard solution of uranium, ^{242}Pu, ^{241}Am, ^{90}Sr-^{90}Y, ^{90}Y, ^{85}Sr, ^{99m}Tc and ^{99}Mo were prepared by spiking the same amount (0.100 mL) of the individual radionuclide solution to 4.2 ml solution of 0.45% NaCl- 0.1mol/l HCl. ^{85}Sr. ^{99m}Tc and ^{99}Mo were measured using γ-spectrometry. For ^{238}U measurement, 1.0 ml of sample solution was diluted for 10 times using 0.5 mol/l HNO_3, and ^{238}U was measured by ICP-MS. For ^{90}Sr-^{90}Y, ^{90}Y, ^{242}Pu and ^{241}Am, the solution was mixed with 10.0 ml of Ultima Gold LLT scintillation cocktail in a 20 ml glass vial, and measured by LSC. By comparison with standard of each radionuclide, the recoveries or decontamination factors of these radionuclides were calculated.

One aliquot of the effluent (2.0 ml) from the anion exchange column was transferred to a beaker, 2.0 mg of stable strontium, 2.0 mg of yttrium and 0.20 ml of 1 mol/l HCl were added. The solution was loaded to a 2ml AG1-×4 anion exchange column (500-100 mesh) and preconditioned with 5 ml of 0.9% NaCl-0.1 mol/l HCl. The beaker was washed 2 times with 1.0 ml of 0.10 mol/l HCl solution and the wash solution was loaded to the column. The effluent and washes were collected and combined in a vial. 2.0 ml of the solution (Effluent+washes) was transferred to a new 20ml glass vial, 10 ml of Ultima Gold LLT scintillation cocktail was added. After mixing, the total alpha activity was measured using LSC by employing α/β discrimination function. The remaining solution was reserved for ^{90}Sr and ^{89}Sr determination.

Purification of strontium for measurement of ^{89}Sr and ^{90}Sr using LSC

For investigation of the recovery of strontium and decontamination factors of ^{99m}Tc/^{99}Tc and ^{99}Mo, 2.0 mL of 8 mol/l HNO_3-0.45% NaCl solution spiked with 2 mg Sr and 2 mg Y carriers and ^{85}Sr, ^{90}Sr-^{90}Y, ^{90}Y, ^{99}Mo or ^{99m}Tc solution was prepared. The solution was loaded to a 2 ml Sr-column pre-conditioned by 10 ml of 8.0 M HNO_3 solution. 10 ml of 8.0 mol/l of HNO_3 solution was used to wash the beaker two times, and the effluent and washes were discarded. Strontium adsorbed on the Sr-resin column was eluted using 10.0 ml of 0.05 M HNO_3 solution, the eluate was collected in a 20 ml glass vial. ^{85}Sr, ^{99m}Tc and ^{99}Mo in the vial were measured using HPGe gamma spectrometry, ^{90}Sr and ^{90}Y were measured by LSC after addition of 10 ml Ultima Gold LLT scintillation cocktail).The chemical recoveries of ^{85}Sr or ^{90}Sr and decontamination factor for ^{90}Y, ^{99}Mo and ^{99m}Tc/^{99}Tc were calculated by compared with the corresponding spiked radionuclide.

2.0 mL of solution of effluent plus wash reserved from the anion exchange separation of ^{99m}Tc eluate was taken to a beaker; concentrated HNO_3 was added to final HNO_3 concentration of 8.0 mol/l. The solution was loaded to a 2 ml Sr-column pre-conditioned by 10 ml of 8.0 M HNO_3 solution. 10 ml of 8.0 mol/l of HNO_3 solution was used to wash the beaker two times. Strontium adsorbed on the Sr-resin column was eluted using 10.0 ml of 0.05 M HNO_3 solution, and collected in a 20 ml glass vial. ^{89}Sr in the eluate was immediately measured by LSC using Cherenkov radiation without scintillation cocktail; the same solution was re-measured after 6-10 day by LSC for Cherenkov counting of ^{90}Y plus ^{89}Sr in order to determine ^{90}Sr in the sample.

Measurement of radionuclides

Measurement of γ- emitters (^{99}Mo, ^{131}I, ^{103}Ru, ^{85}Sr, etc.)

The samples prepared in 2.0 ml of aqueous solution in 20 ml glass vial was directly measured using gamma spectrometry consisting of a HPGe detector, electronic system and Gennie 2000 software for spectrum acquisition and analysis of the gamma spectra (Canberra, Technologies Inc., Meriden, Connecticut, USA). The detector was calibrated for energy and counting efficiency. The relative counting efficiency of the gamma

spectrometry is 38% and the resolution is 1.96 keV for 1332 keV gamma peak of ^{60}Co. ^{99}Mo, ^{131}I, ^{103}Ru and other possible artificial gamma emitters were measured. ^{85}Sr was also measured using this system.

Measurement of ^{89}Sr, ^{90}Sr, ^{242}Pu, ^{241}Am and total alpha emitters

Liquid Scintillation counter, 1200 Quantulus™ (PerkinElmer life Science, Turku, Finland) was used to measure ^{89}Sr, ^{90}Sr and total alpha emitters. Cherenkov counting model was used to measure ^{89}Sr and ^{90}Sr, the separated solution in 0.05 mol/L HNO_3 was directly measured without scintillation cocktail. The procedure blank and the standard solution of ^{89}Sr and ^{90}Sr in the same media were measured with the samples. Each sample was measured 30 min. For ^{242}Pu, ^{241}Am and total alpha emitters, α/β discrimination function was applied, the samples were prepared in 2.0 ml of 0.1 M HCl solution in 20 ml glass vial, 10 ml of Ultima Gold LLT scintillation cocktail was added to each vial for LSC measurement. Different settings of PSA and ^{242}Pu and ^{99}Mo solution (0.45% NaCl-0.1mol/l HCl) were investigated for optimization of counting parameters for alpha emitters by LSC using alpha/beta discrimination. PSA100 was applied for measurement of samples,

Measurement of uranium (^{238}U) using ICP-MS

For investigation of the separation method of uranium isotopes, the separated uranium was diluted in 0.5 mol/L HNO_3, In^{3+} solution was added to a final concentration of 2 ng/ml as internal standard. ^{238}U in the solution was measured by ICP-MS (X series II, Thermo Fisher Scientific, Waltham, MA) equipped with an Xt skimmer cone and a concentric nebulizer, operated under hot plasma conditions. The detection limit of this instrument for ^{238}U is 0.001 ng/mL.

Results and discussion

Removal of ^{99m}Tc for measurement of γ emitters

^{99m}Tc decays by isomeric transition to ^{99}Tc with a relative short half-life of 6.02 h and emits γ-ray of 140.5 keV (89%). Because the activity of ^{99m}Tc is normally 3-10 orders of magnitude higher than other γ-emitting radionuclides in the ^{99m}Tc eluate, ^{99m}Tc has to be removed before measurement of other gamma emitters in a relative good detection limit. Lead shielding of the sample has been applied to measure ^{99}Mo based on the low γ-energy of ^{99m}Tc (140.5 keV). [5,6,7]. However, the dead shied also reduces the counting efficiency of other gamma emitters, consequentially worsen their detection limits. Therefore, it is no suitable for sensitive measurement of radionuclides (e.g. ^{131}I, ^{103}Ru). Chemical separation of technetium might be an option, but the chemical property of technetium is similar to ruthenium and molybdenum, it is not easy to chemically remove technetium, but not Ru, Mo, I and other gamma emitters. Due to the shorter half-life of ^{99m}

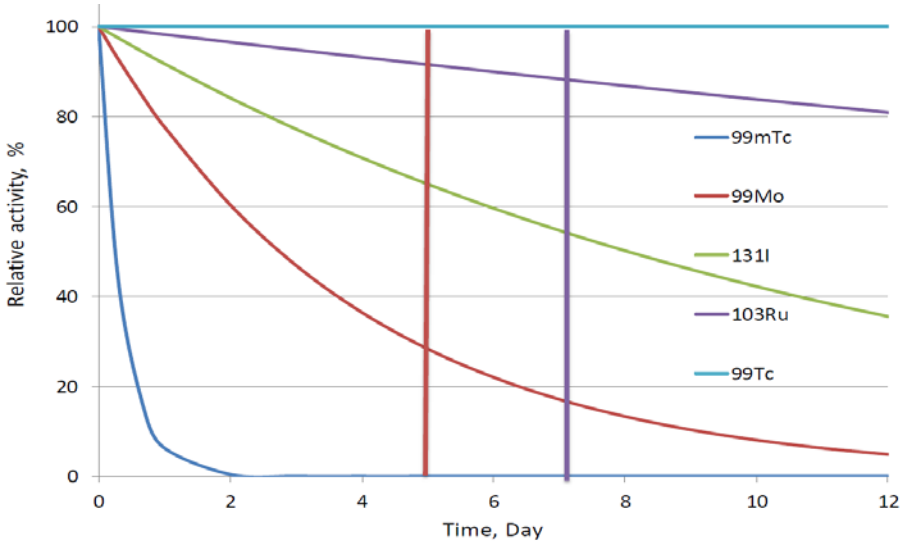


Fig. 2 Variation of radioactivity of ^{99m}Tc, ^{99}Mo, ^{131}I and ^{103}Ru with decay time

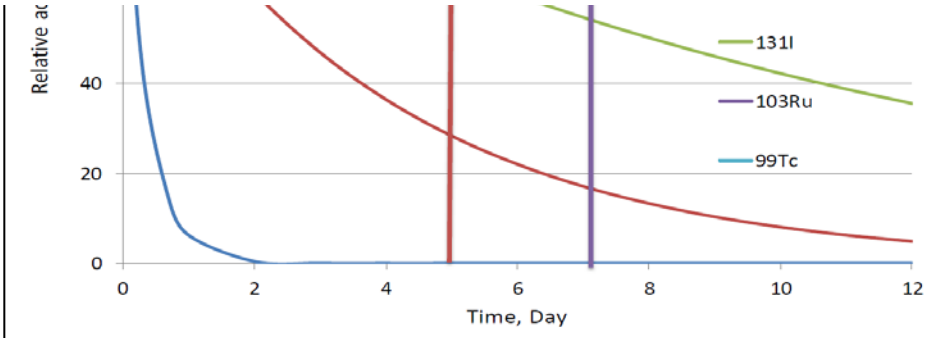


Fig. 2 Variation of radioactivity of ^{99m}Tc, ^{99}Mo, ^{131}I and ^{103}Ru with decay time

By this method, ^{99m}Tc can be efficiently removed, enable to measure low level of γ-emitting impurity radionuclides. Fig. 3 shows a gamma spectrum of ^{99m}Tc eluate of 2.5 G a 9 ^{1}I, 3 he d he s

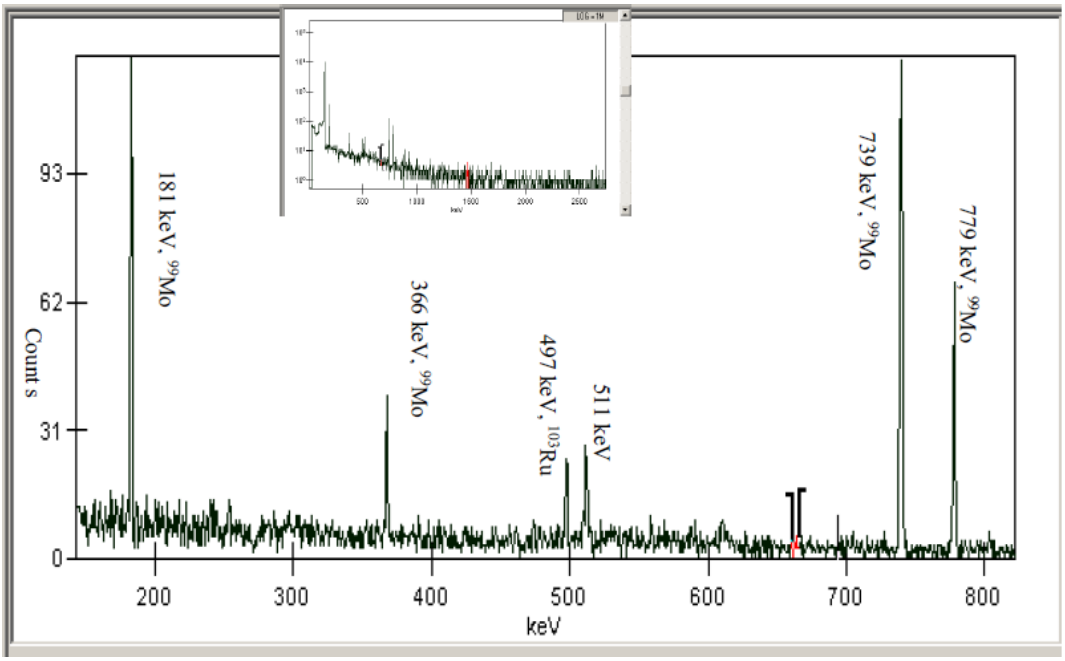


Fig. 3 Gamma spectrum of ^{99m}Tc eluate of 2.5 GBq after 5 days decay, showing the measurable ^{99}Mo and ^{103}Ru.

Separation of ^{99}Mo and ^{99}Tc/^{99m}Tc for measurement of alpha emitters by LSC

In ^{235}U fission produced ^{99}Mo, alpha emitters are principally uranium and its long-lived activation products, including ^{237}Np, ^{238}Pu, ^{239}Pu, ^{240}Pu, and ^{241}Am. Tedious chemical separation procedure including solvent extraction, ion exchange chromatography, electrodeposition and alpha spectrometry measurement method have been applied for determination of plutonium [12]. An individual separation or a combined separation method is needed for other alpha emitting radionuclides. An extraction scintillator has

been proposed to extract both plutonium and americium for the measurement of total alpha emitters using LSC [11]. However, ^{99}Mo and ^{90}Y can be also extracted to the scintillator, which significant worsens the detection limit of alpha emitters because of the spillover of beta emission of ^{99}Mo into alpha window, especially for samples with relative high ^{99}Mo. A simple single step anion exchange chromatographic method was proposed in this work for separation of ^{99}Mo and ^{99m}Tc from the ^{99m}Tc eluate. This is based on non-adsorption of actinides (U, Np, Pu, Am, Cm) on strong anion exchange resin at neutral or diluted HCl acid, where Tc and Mo, as well as other anions such as ^{131}I (iodide or iodate) and Ru (RuO_4^-), can be strongly absorbed on the column. The experiment using spiked solution (simulating the ^{99m}Tc eluate) shows that the decontamination factors are 5×10^3 for ^{99}Mo and 5×10^4 for ^{99m}Tc, while the recoveries of U, Pu and Am are more than 83% in 2 ml of effluent and 2 ml wash (Table 2). The slightly lower recovery is attributed to the small volume of 0,1 mol/l HCl wash solution. When the column was washed with 10 ml of 0.1 mol/l HCl, the recovery of U, Pu and Am are higher than 95%. In this work, only 2 ml of 0.1 mol/l HCl was used to wash the column and an average recovery for alpha emitters (U, Np, Pu and Am isotopes) of (84.2±4.0)% was used for calculation of the total alpha activity in the ^{99m}Tc eluate. It should be mentioned that ^{99}Tc can also cause interference for the total alpha measurement by LSC through spillover to alpha window. Besides from ^{99m}Tc, ^{99}Tc is also formed through direct decay of ^{99}Mo, which is accumulated in the generator column. Due to the long half-life of ^{99}Tc (211.1 kyr), the activity level of ^{99}Tc is normally low in the ^{99m}Tc eluate. A long accumulation time might cause an increased level of ^{99}Tc in the ^{99m}Tc eluate. For 10 GBq ^{99}Mo-^{99m}Tc generator, ^{99m}Tc eluate might contain 250Bq ^{99}Tc after 2 days accumulation, this might cause a contribution to the alpha window due to spillover of ^{99}Tc counts, and causing an increased detection limit for total alpha emitters. The separation method using anion exchange chromatography can also remove ^{99}Tc in the ^{99m}Tc eluate, so reducing its influence in the LSC measurement of total alpha emitters. The detection limit of this method for total alpha is calculated to be 0.05 Bq. However, the detection limit of total alpha can be degraded when high content of ^{99}Mo in the sample due to the spillover of ^{99}Mo counts to alpha window. For a ^{99m}Tc eluate containing 5GBq ^{99m}Tc and 5MBq ^{99}Mo, the separated solution for total alpha

measurement still contain about 300 Bq of ^{99}Mo after 5 days decay and anion exchange chromatographic separation with a decontamination factor of 5.1×10^{3}. This might cause an increased counts up to 190 CPM in the alpha window, corresponding to an increased detection limit of 6 Bq, which is higher than the required limitation of 1×10^{-9} for ratio of total alpha to ^{99m}Tc activity in pharmacopoeias [3,4]. In this case, two anion exchange chromatographic columns are applied to enable to achieve a decontamination factor of 2.5×10^{5} for Mo, which enable to improve the detection limit of alpha emitters to 0.12 Bq, corresponding to a ratio of 2.4×10^{-11} to ^{99m}Tc.

Table 2 Chemical recoveries of U, Pu and Am and decontamination factors of Mo and Tc in the anion exchange separation procedure.

Redionuclide	Recovery , % [1)]		Decontamination factor [2)]	
	2 ml wash	10 ml wash	2 ml wash	10 ml wash
^{238}U	84.1±3.1	96.7±3.4		
^{242}Pu	83.8±3.5	95.2±3.5		
^{241}Am	84.5±3.6	96.5±3.8		
^{99m}Tc			$(5.5\pm0.4)\times10^{4}$	$(3.7\pm0.8)\times10^{4}$
^{99}Mo			$(5.1\pm0.8)\times10^{3}$	$(3.8\pm1.2)\times10^{3}$

1) Recovery of actinides in the effluent and 0.1 mol/l HCl wash

2) The ratio of the ^{99m}Tc and ^{99}Mo in the effluent and wash to their amount in the original ^{99m}Tc eluate.

Separation and purification of radiostrontium for measurement of low level ^{89}Sr and ^{90}Sr

For measurement of low level ^{89}Sr and ^{90}Sr in the ^{99m}Tc eluate, all other radionuclides have to be removed with high decontamination factors, especially for ^{99m}Tc and ^{99}Mo which are very high radioactivity compared to ^{89}Sr and ^{90}Sr in the ^{99m}Tc eluate, a decontamination factors of more than 10^{7} in total are required.

In the separation procedure using anion exchange chromatography, strontium as Sr^{2+} is not adsorbed on the column and collected in the effluent and 0.1 mol/l HCl wash. The

tracer experiment using ^{85}Sr and ^{90}Sr shows that the recovery of strontium is more than 98%, ^{90}Y also showed a recovery of more than 99% in this step (Table 3).

For further purification of radiostrontium, a specific extraction chromatographic column, Sr spec column (2ml) was applied. The tracer experiment showed that radiostrontium can be quantitatively separated with a recovery of more than 98%. While the decontamination factor of Sr-column is more than 5×10^5 for ^{99m}Tc and ^{99}Mo (Table 3). The overall decontamination factors for ^{99m}Tc and ^{99}Mo by two steps chromatographic separation reach to more than 1×10^8. Considering the removal of ^{99m}Tc by radioactive decay, the removal efficiency for ^{99m}Tc should reaches to more than 1×10^{13} for 7 days decay. For a ^{99m}Tc eluate containing 10 GBq ^{99m}Tc and 1 MBq ^{99}Mo, the detection limits of the method are 0.5 Bq for ^{89}Sr and ^{90}Sr, corresponding to a limitations 5×10^{-11} for ^{89}Sr and ^{90}Sr, more than 3 orders of magnitude lower than the required limitation in the pharmacopoeias [3,4].

Table 3 Chemical recoveries of strontium and decontamination factors of Mo and Tc in the chemical separation procedure for ^{89}Sr and ^{90}Sr measurement

Nuclide	Recovery , %			Decontamination factor [1)]		
	AG1×-4	Sr-coulmn	Total	AG1×-4	Sr-coulmn	Total
^{85}Sr	98.6±2.3	99.5±1.5	98.0±2.5			
^{90}Sr	99.2±1.3	98.2±2.5	97.7±2.8			
^{90}Y	99.7±1.6	< 0.5	<0.5			
^{99m}Tc				$(5.5\pm0.4)\times10^4$	$(8.6\pm1.2)\times10^5$	$(2.6\pm0.6)\times10^9$
^{99}Mo				$(5.1\pm0.8)\times10^3$	$(5.7\pm1.8)\times10^5$	$(1.2\pm0.4)\times10^8$

1) The ratio of the ^{99m}Tc and ^{99}Mo in the separated solution to the amount in the original ^{99m}Tc eluate.

Interference of beta emitters on the measurement of total alpha emitters by LSC using α/β discrimination function.

Based on the different pulse decay time of alpha particles and beta particles in LSC, alpha particles can be measured by LSC using the build-in pulse shape analysis (PSA) or time resolved pulse decay analysis function in most of commercial LSC instrument. However, it is impossible to completely avoid mis-discrimination of beta to alpha, or alpha to beta window, selection of suitable PSA parameter is critical for obtaining reliable result and low [illegible] re spiked to [illegible] ixed with scin [illegible] rent SPA valu [illegible] lition, the spil [illegible] ed to less than

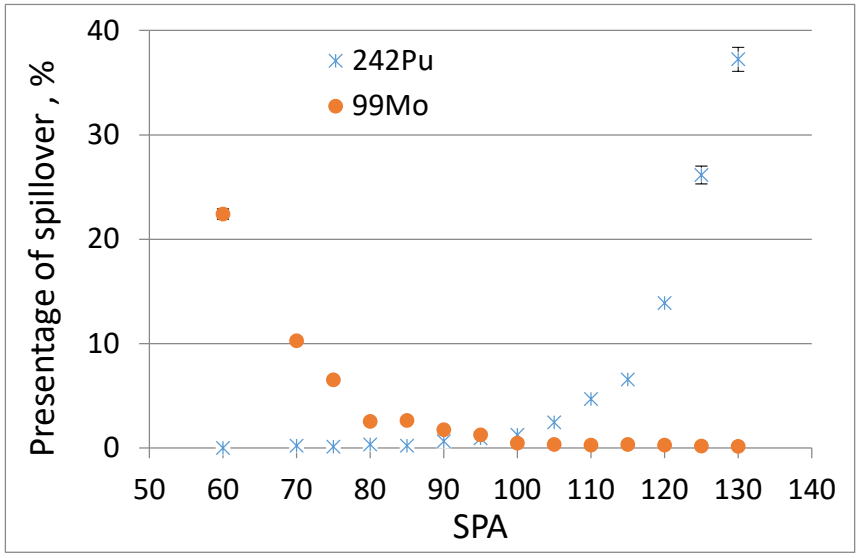
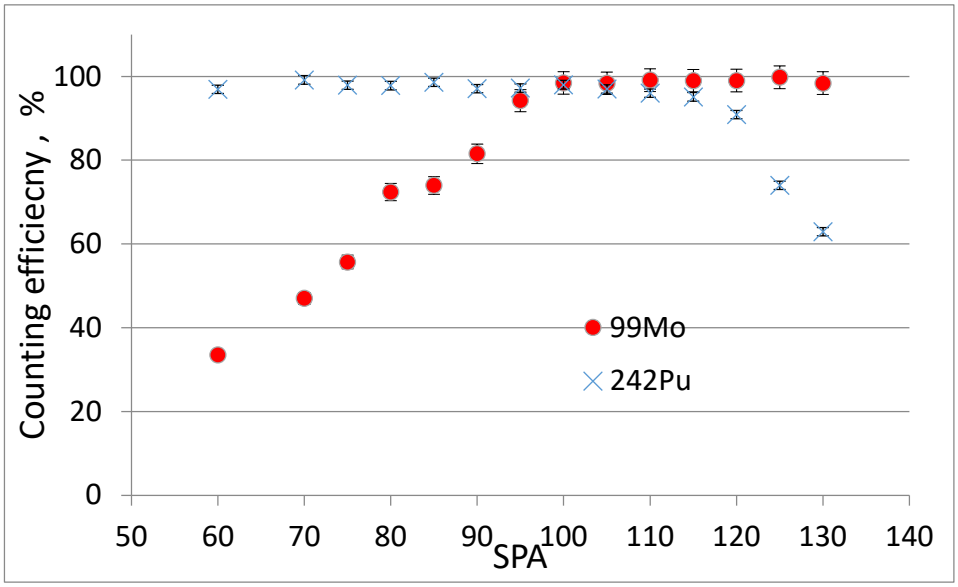


Fig. 4 Spillover of ^{99}Mo to alpha window and ^{242}Pu to beta window at different PSA settings



Measurement of ^{89}Sr and ^{90}Sr by LSC using Cherenkov counting

^{89}Sr and ^{90}Sr are pure beta emitters with different energies, when both of them exist in the sample, two times Cherenkov counting or one LSC and one Cherenkov counting can be used for their measurement [14]. In this work, two times Cherenkov counting was applied for measurement of ^{89}Sr and ^{90}Sr. The first measurement was implemented immediately after Sr-resin column separation. In this case, the measured counts mainly resulted from the beta particle of ^{89}Sr with maximum energy of 1495 keV, the contribution of ^{90}Sr is very small due to its low energy (Emax = 546 keV). With 10 ml of 0.05 mol/l HNO_3 eluate of strontium from the Sr-column, the Cherenkov counting efficiency of ^{89}Sr was (34.5±1.1)%, while only less than 1% for ^{90}Sr. ^{90}Sr decays to ^{90}Y, which is also a pure beta emitter with a high beta energy (Emax=2280 keV), and can be measured by Cherenkov counting. The counting efficiency of ^{90}Y by Cherenkov counting using Quantulus 1220 LSC was measured to be (58.0±1.5)%, which will cause a contribution to the ^{89}Sr measurement, if ^{89}Sr is counted a relative longer time after the Sr- column separation. It can be calculated that about 2.1 % and 5.2 % of ^{90}Sr (through ^{90}Y) is counted after 2 hours and 5 hours of the separation, respectively. Therefore, it is better to count ^{89}Sr within 5 hours after the separation. The contribution of ^{90}Sr (through ^{90}Y) has to be corrected, if ^{89}Sr measurement was conducted more than 2 hours after the separation.

^{90}Sr in the separated strontium fraction was measured 7-10 days after then separation through Cherenkov counting of ^{90}Y grown from ^{90}Sr. Due to the relative short half-life of ^{90}Y (64 h), the activity of ^{90}Y is 83.8 % of the ^{90}Sr activity after 7 days ingrowth. Because ^{89}Sr remains in the separated strontium samples, it is also counted through ^{90}Y. Although the Cherenkov spectrum of ^{90}Y slightly expended to high-energy direction, but very high overlapped with the spectrum of ^{89}Sr (Fig. 6). The measured counts is the sum of ^{90}Y and ^{89}Sr, the ^{90}Sr activity was calculated by subtraction of the ^{89}Sr contribution and for the ingrowth of ^{90}Y (not reaching equilibrium between ^{90}Y and ^{90}Sr).

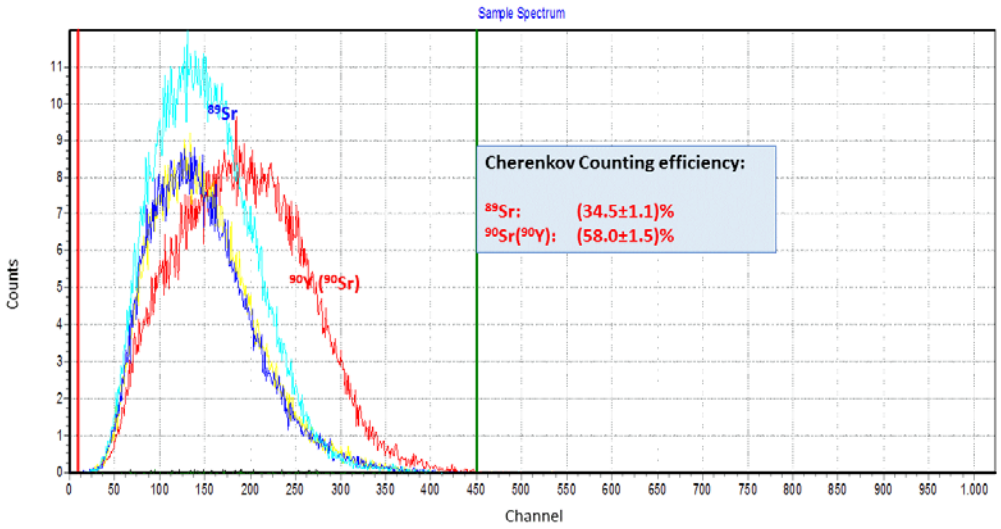


Fig. 6 Spectra of ^{89}Sr and ^{90}Y(^{90}Sr) by Cherenkov counting

Analytical accuracy and detection limit

In order to confirm the analytical accuracy of the developed method for determination of the beta and alpha emitters, standard addition method was used. A 10 ml ^{99m}Tc eluate taken from a 10 GBq ^{99}Mo-^{99m}Tc generator was divided into two 5 ml aliquots, one

aliquot was used for direct analysis, another aliquot was spiked with ^{89}Sr, ^{90}Sr and ^{242}Pu and analyzed using the developed method. The results (Table 4) show that the measured values of ^{89}Sr, ^{90}Sr and total alpha are in a good agreement with the spiked values ($p<0.01$), confirmed that the developed method is accurate.

Table 4 Analytical results of ^{99m}Tc eluate with standard addition of ^{89}Sr, ^{90}Sr and ^{242}Pu

Radionuclide	5 ml ^{99m}Tc elute	5ml ^{99m}Tc eluate with spikes	
	Bq	Spiked value, Bq	Analyzed value, Bq
^{89}Sr	0.16±0.02	5.21±0.12	5.28±0.35
^{90}Sr	0.20±0.06	8.15±0.15	8.38±0.43
Total alpha (^{242}Pu)	<0.05	1.25±0.04	1.27±0.07

Table 5 listed the calculated detection limit of the method for each radionuclide. For gamma emitters, these values are calculated based on 7 days decay time and the content less than 5 kBq ^{99}Mo in 10 GBq ^{99m}Tc eluate at the beginning, which are often situation in the routine quality control analysis of ^{99m}Tc eluate in ^{99m}/^{99m}Tc generator products in our lab. For a sample with high ^{99}Mo content, the detection limits for ^{131}I, ^{103}Ru and other gamma emitters will be higher than the values listed.

Table 5 Detection limits of the analytical method for the impurity radionuclides in ^{99m}Tc eluate from fission ^{99}Mo/^{99m}Tc generator

Radionuclide	Measurement method	Detection limit [1)], Bq	Limitation by Eu Ph. [2)], Bq
^{99}Mo	γ-spectrometry	20	5.0×10^{6}
^{131}I	γ-spectrometry	4.5	2.5×10^{5}
^{103}Ru	γ-spectrometry	3.0	2.5×10^{5}
^{89}Sr	LSC/Cherenkov counting	0.5	3.0×10^{3}
^{90}Sr	LSC/Cherenkov counting	0.5	3.0×10^{2}

Total alpha	LSC/α/β discrimination	0.05	5.0

1) For a decay time of 7 days, and 30 min counting time for gamma spectrometry and LSC.
2) For a ^{99m}Tc eluate of 10 GBq

Analytical results of ^{99m}Tc eluates from some batchs of ^{99}Mo/^{99m}Tc generators

The deveoped method has been used for the routine analysis of ^{99m}Tc eluate from ^{99}Mo/^{99m}Tc generators for radionuclidic impurity as part of the quality ontrol of the ^{99}Mo/^{99m}Tc generator in our lab. Table 6 shows the analytical results of ^{99m}Tc eluate from 4 batches of ^{99}Mo/^{99m}Tc generators. The measured radionuclidic impurities are lower than the limitation of Eu. Ph. In some samples, the ^{99}Mo content was relative high, up to 0.7 MBq in 1.0 GBq of ^{99m}Tc eluate, indicating ^{99}Mo the major impurity radionuclide. But this level is still much lower than the limitation of 0.1% of the ^{99m}Tc radioactivity in the European phamarcopoeia [3].

Table 6 Analytical results of impurity radionculides in ^{99m}Tc eluate from some batches of ^{99}Mo/^{99c}Tc generators for quality control

Radionuclide	Concentration of radionuclide in ^{99m}Tc eluate from different batches			
	Batch 1	Batch 2	Batch 3	Batch 4
^{99m}Tc, GBq	3.87±0.06	5.27±0.07	5.62±0.09	1.02±0.03
^{99}Mo, kBq	48.0±3.5	105±7	275±18	705±25
^{131}I, Bq	< 4.0	5.60±3.2	175±32	12.4± 6.8
^{103}Ru, Bq	< 3.0	<3.0	90±35	<3.0
^{89}Sr, Bq	<0.25	<0.32	<0.24	<0.50
^{90}Sr, Bq	<0.30	<0.41	<0.25	< 0.50
Total alpha, Bq	0.06±0.03	<0.05	0.13±0.07	<0.05

Uncertainties presented in the analytical results are expanded uncertainties using a coverage factor k=2, which was estimated considering all possible contributions. For γ-emitters, the uncertainty mainly come from the statistic error of gamma rays counting, spectra interference especailly from high level of ^{99}Mo, efficiency calibration, and sample

weight. For ^{89}Sr and ^{90}Sr, the uncertainty mainly comes from the statistic error of LSC counting, counting efficiency calibration, procedure blank, recovery in the chemical separation steps (anion exchnage and Sr-column chromatography) and sample weigh. For total α-emitters, the statistic error of LSC counting of alpha emitters in sample, blank and standard, spillover of beta counts to alpha window, counting efficiency, recovery of alpha emitter in chemcial separation and sample weight.

In all samples, the content of radiostrontium and total α-emitters are very low, close to the detection limit, causing the analytical uncertainties are relative high, this is mainly becasue of the counting uncertainty for samples and blanks.

Conclusions

A sequentially analytical method was developed for simultaneous determination of radionuclidic impurities in ^{99m}Tc eluate for quality control of ^{99}Mo/^{99m}Tc generator, including ^{99}Mo, ^{131}I, ^{103}Ru, other gamma emitters, ^{89}Sr, ^{90}Sr and total α-emitters. The results show that this method can well meet the requirement of quality control of ^{99}Mo/^{99m}Tc generators according the limitation of European pharmacopoeia. The main findings and achievements are listed below:

1) Radioactive decay is an effective and useful method for removal of ^{99m}Tc for measurement of gamma emitting radionuclides, 7 days decay can remove ^{99m}Tc by a factor of 2.7×10^{8}, which enable measurement of ^{131}I and ^{103}Ru down to 4.5 and 3.0 Bq and ^{99}Mo of 20 Bq.

2) ^{99}Mo is the major radionuclidic impurity in ^{99m}Tc eluate from the ^{99}Mo/^{99m}Tc generator, the high ^{99}Mo content in the sample degrades the detection limit of other gamma emitters. For a ^{99m}Tc eluate containing 5 MBq of ^{99}Mo content, the detection limit of ^{131}I, ^{103}Ru and other gamma emitters will be worsened to 20 Bq.

3) ^{99}Mo and ^{99m}Tc/^{99}Tc are the major interference for the measurement of pure beta and alpha emitters using LSC and have to be removed by chemical separation. Strong basic anion exchange chromatography is confirmed an effective method for removal

of Mo and Tc with a decontamination factor of 5×10^3 and 5×10^4, respectively, while the possible alpha emitters (U, Pu, Np, Am and Cm isotopes) and strontium can be highly recovered. For high ^{99}Mo content sample, a two-column separation is needed for obtaining a better detection of total alpha emitters, which is influenced by ^{99}Mo through spillover to alpha window in LSC measurement.

4) A further purification of strontium using a specific Sr-column is proposed enabling to obtain a pure strontium solution for measurement of ^{89}Sr and ^{90}Sr in a low level. With the established method, the decontamination factors for ^{99}Mo and ^{99}Tc are higher than 1×10^8. Considering the removal of ^{99m}Tc by radioactive decay, this is sufficiently good for the determination of ^{89}Sr and ^{90}Sr down to 0.5 Bq in the ^{99m}Tc eluate.

Acknowledgements

The author acknowledges prof. Mikael Jensen and Dr. Sven P. Nielsen from DTU Nutech doe their suggestions and discussion of during the method development. Dr. Dannis Ringkjøbing Elema helped to obtain and calibrate radionuclide standards.

References

1. Zolle I (2007). Technetium-99m pharmaceuticals, Preparation and quality control in nuclear medicine, Springer Berlin Heidelberg, New York

2. Takács S, Szűcs Z, Tárkányi F, Hermanne A, Sonck M (2003) Evaluation of proton induced reactions on ^{100}Mo: New cross sections for production of ^{99m}Tc and ^{99}Mo. J Radioanal Nucl Chem. 257 (1): 195–201

3. Directorate for the Quality of Medicine and Healthcare, Council of Europe (2014), Sodium pertechnetate (^{99m}Tc) injection (fission), European Pharmacopoeia-8.0, Strasbourg Cedex, France, p 1090, http://online6.edqm.eu/ep800/

4. United States Pharmacopeial Convention (2005), Official Monographs: USP 28, Sodium pertechnetate Tc-99m injection. United States Pharmacopeia (USP) 28 (NF) 23, p 1861.

5. Andrade W G, Lima F F (2009) Evaluation of the eluate quality of ^{99}Mo-^{99m}Tc generator in Receife, Brazil, International Nuclear Atlantic Conference - INAC 2009, 27th Sept. – 2nd Oct. Rio de Janeiro, Brazil.

6. UAMS, College of Pharmacy, Nuclear pharmacy, Quality control procedure for free pertechnetate-99m, http://nuclearpharmacy.uams.edu/proc1.htm

7. Hammermaier A, Reich E, Bögl W (1986) Chemical, radiochemical and radionuclidic purity of eluates from different commerical fission ^{99}Mo/^{99m}Tc generators. Eur J Nucl Med. 12:41-46

8. Sodd VJ, Fortman DL (1976) Analysis of the ^{89}Sr and ^{90}Sr content in eluates of fission produced ^{99}Mo-^{99m}Tc generator. Health Physics. 30(2):179-182

9. Khan M, Jabbar T, Asif M, Anjum MI, Dilband M, Khan K, Jabbar A, Arshed W (2014) Radiostrontium separation from sodium molybdate solution and its measurement using LSA: an application to radiopharmaceutical analysis, J Radioanal Nucl Chem. 299:577-582

10. Braun H, Hoffmann P, Lieser KH (1981) Determination of alpha and pure beta emitting impurities in ^{99}Mo/^{99m}Tc generator eluates. J Radioanal. Chem. 67(1): 215-220

11. Terlikowska T, Hainos D, Cassette P, Radosewski T (2000) Application of α/β discrimination in liquid scintillation counting for the purity control of ^{99m}Tc medical solutions, Appl Radiat Iso. 52:627-632.

12. Johansson L, Mattsson S (1980) Plutonium in technetium-99m labeled pertechnetate for clinic use. J Nucl Med. 21(11):1091-1094.

13. Directorate for the Quality of Medicine and Healthcare, Council of Europe (2014), Sodium molybdate (^{99}Mo) solution (fission), European Pharmacopoeia-8.0, Strasbourg Cedex, France, p 1088.

14. Lehto J, Hou XL (2010) Chemistry and Analysis of RadionuclidesWiley-VCH, Weinheim,